ARSENICAL-RESISTANCE IN THE AFRICAN TRYPANOSOME.

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Melarsoprol, a trivalent melaminophenyl arsenical, is used in the treatment of late stage African sleeping sickness, a disease caused by parasitic protozoa of the *Trypanosoma brucei* subgroup. Employing a simple spectrophotometric assay, which measures the decrease in absorbance at 750 nm due to cell lysis, a number of physiological compounds were investigated for their effects on melarsen oxide-induced lysis in a cloned line of *T. brucei*. Only the purines, adenine and adenosine were able to significantly delay the trypanolytic effects of melarsen oxide, via competition for an adenosine transporter. Investigation of adenosine transport in *T. brucei* has identified two transporters, a P1 (K_m 0.15 μM, V_{max} 10.6 pmol/10^8 cells/sec) which also recognises other purine ribonucleosides and a P2 (K_m 0.59 μM, V_{max} 9.5 pmol/10^8 cells/sec) which also recognises the purine base, adenine (Ki 0.38 μM). P2 adenosine transport is inhibited by the trivalent melaminophenyl arsenicals, melarsen oxide and melarsoprol (K_i 0.28 μM).

The possibility that resistance to the trivalent melaminophenyl arsenical drugs may be due to a loss of uptake by the P2 transporter into the cell, was investigated in a derived melarsen-resistant clone. P2 adenosine transport was found to be absent in the melarsen-resistant line, suggesting that this clone has also lost the ability to transport melaminophenyl arsenicals.

Cross-resistance between the melaminophenyl arsenicals and another class of trypanocide, the diamidines, has been reported in several cases. Therefore we investigated whether the diamidine drugs are also transported by the P2. Inhibition studies have demonstrated that berenil, propamidine and pentamidine all inhibit P2 adenosine transport (K_i for pentamidine 0.48 μM), and are all able to inhibit the trypanolytic effects of melarsen oxide *in vitro*, suggesting that the diamidines also compete for uptake by the P2 transporter.

In addition to the kinetic studies the structural requirements necessary for recognition by the P2 transporter have been identified, with a view to targeting other less toxic trypanocidal agents into melarsen-sensitive trypanosomes.

Source: https://www.industrydocuments.ucsf.edu/docs/rfmv0000